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Review

Gonadal hormones and the control of reactive gliosis

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ABSTRACT

This article is part of a Special Issue "Hormones & Neurotrauma".

Astrocytes and microglia respond to central nervous system (CNS) injury with changes in morphology, proliferation, migration and expression of inflammatory regulators. This phenomenon is known as reactive gliosis. Activation of astrocytes and microglia after acute neural insults, such as stroke or traumatic CNS injury, is considered to be an adaptive response that contributes to minimize neuronal damage. However, reactive gliosis may amplify CNS damage under chronic neurodegenerative conditions. Progesterone, estradiol and testosterone have been shown to control reactive gliosis in different models of CNS injury, modifying the number of reactive astrocytes and reactive microglia and the expression of anti-inflammatory and proinflammatory mediators. The actions of gonadal hormones on reactive gliosis involve different mechanisms, including the modulation of the activity of steroid receptors, such as estrogen receptors α and β, the regulation of nuclear factor-κB mediated transcription of inflammatory molecules and the recruitment of the transcriptional corepressor c-terminal binding protein to proinflammatory promoters. In addition, the Parkinson's disease related gene parkin and the endocannabinoid system also participate in the regulation of reactive gliosis by estradiol. The control exerted by gonadal hormones on reactive gliosis may affect the response of neural tissue to trauma and neurodegeneration and may contribute to sex differences in the manifestation of neurodegenerative diseases. However, the precise functional consequences of the regulation of reactive gliosis by gonadal hormones under acute and chronic neurodegenerative conditions are still not fully clarified.

Contents

Introduction

The brain and the endocrine glands maintain a permanent cross-talk to regulate the homeodynamic equilibrium in the organism. The brain modulates the activity of the endocrine glands and in turn, hormonal secretions regulate the function of the central nervous system not only under physiological conditions but also under disease states (Garcia-Segura, 2009). Accordingly, several hormones have been shown to modulate the response of neural tissue to injury and to exert protective or reparative roles in the central nervous system (CNS). Among these hormones, the neuroprotective actions of gonadal steroids have received considerable attention and the mechanisms involved in these actions have been studied with considerable detail.

Neurons are direct targets for the neuroprotective actions of gonadal steroids. Indeed, studies in primary neuronal cultures, in

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absence of glial cells, have shown that gonadal hormones exert direct protective actions on neurons. However, *in vivo*, gonadal hormones coordinate neuron–glia interactions (Garcia-Ovejero et al., 2005; McAsey et al., 2006; Struble et al., 2007; Azcoitia et al., 2010) and have complementary neuroprotective mechanisms, acting on the neurovascular unit and regulating reactive gliosis and neuroinflammation (Garcia-Estrada et al., 1993; Barreto et al., 2007; Brown et al., 2010; Saraceno et al., 2010; Labombarda et al., 2011).

Reactive gliosis is a complex phenomenon involving the activation and proliferation of microglia and astroglia and the migration of these cells towards the sites of injury (Sofroniew, 2009; Graeber and Streit, 2010; Lull and Block, 2010). Other cell types, such as endothelial cells, NG2 cells and oligodendrocytes are also affected by neurodegenerative stimuli and by the activity of astrocytes and microglia. In addition, the activation of astrocytes and microglia during reactive gliosis is accompanied with modifications in the local release of chemokines and cytokines, which regulate the inflammatory process. Reactive astrocytes suffer a continuum of progressive and multiple modifications in gene expression and cellular morphology that depend on the cellular context and the severity of the insult (Sofroniew, 2009; Sofroniew and Vinters, 2010). These modifications, which involve gain and loss of cellular functions, may have both beneficial and detrimental effects on the surrounding tissue. The progression in the process of astrogliosis, which is regulated by multiple extracellular signals and multiple intracellular signaling cascades (Sofroniew, 2009; Sofroniew and Vinters, 2010), may turn a neuron-protective astrocyte into a proinflammatory, neuron-damaging cell. Acute reactive gliosis and acute inflammation are considered adaptive responses that contribute to minimize neuronal damage. However, chronic gliosis and inflammation may enhance neuronal damage and amplify the neurodegenerative process (Sofroniew, 2009; Graeber and Streit, 2010; Lull and Block, 2010). It is therefore important to understand how reactive gliosis and local inflammation are regulated in the CNS and to identify the factors involved in this regulation. In this review we will focus on the role of gonadal hormones as regulatory factors of the process of microgliosis, astrogliosis and local inflammation in the CNS.

Control of reactive gliosis by progesterone

It is well documented that progesterone exerts neuroprotective actions in the brain and the spinal cord under different pathological conditions, such as traumatic brain injury, spinal cord transection, multiple sclerosis and stroke (Garay et al., 2007, 2008, 2009; De Nicola et al., 2009; Sayeed and Stein, 2009; Stein and Wright, 2010; Feeser and Loria, 2011; Hussain et al., 2011; Labombarda et al., 2011). Part of the neuroprotective actions of progesterone may involve the control of reactive gliosis and the inflammatory response of glial cells, upregulating anti-inflammatory cytokines and downregulating proinflammatory mediators (Sayeed and Stein, 2009; Stein and Wright, 2010; Yates et al., 2010; Feeser and Loria, 2011). For instance, progesterone reduces the production of nitric oxide and the expression of inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, in cultured microglia exposed to lipopolysaccharide (LPS) (Drew and Chavis, 2000; Jiang et al., 2011). *In vivo* studies have shown that progesterone alone (Jiang et al., 2011), or in combination with estradiol (Dang et al., 2011), reduces the activation of microglia in experimental models of stroke in rats. Progesterone reduces also the proliferation and the size of GFAP immunoreactive astrocytes and regulates local brain inflammatory response after traumatic or penetrating brain injury in rats (Garcia-Estrada et al., 1993, 1999; Djebaili et al., 2005; VanLandingham et al., 2007; Feeser and Loria, 2011). Similar effects have been obtained with its precursor pregnenolone (García-Estrada et al., 1999). Progesterone also reduces reactive astroglia and reactive microglia after spinal cord transection (Labombarda et al., 2011). Reduction of astrogliosis by progesterone has been also detected in the spinal cord of Wobbler mouse (Meyer et al., 2010), an animal model of motoneuron degeneration. Furthermore, progesterone reduces microglia activation in a model of demyelination in the spinal cord (Garay et al., 2011). Therefore, the actions of progesterone on different experimental models of CNS pathology involve the control of reactive astroglia and reactive microglia.

Control of reactive gliosis by androgens

Protective actions of androgens have been identified in some neurodegenerative diseases such as multiple sclerosis (Gold and Voskuhl, 2009), Alzheimer's disease (Pike et al., 2009) and focal cerebral ischemia (Pan et al., 2005; Uchida et al., 2009). Androgens also protect motoneurons from axotomy (Fargo et al., 2009). However, detrimental neurological effects of androgens have also been described after brain ischemia (Yang et al., 2002; Cheng et al., 2007; Nakano et al., 2010) and androgens increase damage in spinal and bulbar muscular atrophy, a disorder caused by abnormal polyglutamination of androgen receptor and characterized by spinal cord and brain stem motoneuron loss (Parodi and Pennuto, 2011). The actions of androgens on reactive gliosis have not been systematically explored yet. However, available evidence indicates that testosterone decreases reactive astroglia and reactive microglia after a stab wound injury in the brain (Garcia-Estrada et al., 1993, 1999; Barreto et al., 2007). Testosterone also decreases astrogliosis associated to motoneuron axotomy (Coers et al., 2002; Storer and Jones, 2003).

The adrenal androgen and testosterone precursor, dehydroepiandrosterone (DHEA), also regulates reactive gliosis. DHEA reduces the inflammatory response in LPS-stimulated microglia (Wang et al., 2001) and mycoplasma-stimulated astrocytes (Kipper-Galperin et al., 1999). *In vivo*, it has been shown that DHEA reduces microglia activation in the striatum in a rat model of Parkinson's disease (Tomas-Camardiel et al., 2002) and downregulates astrogliosis after a penetrating brain injury (García-Estrada et al., 1999) and after denervation of the olfactory bulb (Hoyk et al., 2004).

Control of reactive gliosis by estradiol

Neuroprotective actions of estradiol have been characterized in numerous experimental models of neurodegenerative diseases *in vitro* and *in vivo* (Garcia-Segura et al., 2001; Bourque et al., 2009; Lebesgue et al., 2009; Pike et al., 2009; Azcoitia et al., 2011; Scott et al, 2012). In several of these models the hormone has been shown to regulate the number of reactive microglia and the number of reactive astrocytes. For instance, estradiol reduces microglia reactivity after traumatic injury of the brain (Barreto et al., 2007) or the spinal cord (Sribnick et al., 2005), after the intracerebroventricular or the systemic administration of LPS (Vegeto et al., 2001, 2003, 2006, 2008; Tapia-Gonzalez et al., 2008) and after the experimental induction of central demyelination by the administration of cuprizone (Taylor et al., 2010). Microglia reactivity is also reduced after estradiol treatment in the oculomotor nucleus after peripheral axotomy (Gyenes et al., 2010), in the substantia nigra pars compacta in a mouse model of Parkinson's disease (Tripanichkul et al., 2006) and in the brain of APP23 mice, an Alzheimer's disease model (Vegeto et al., 2006). The hormone not only reduces the number of activated microglia but also their response to inflammatory stimuli, such as LPS or pro-inflammatory cytokines, decreasing their phagocytic activity and the production of TNFα and inducible nitric oxide (Drew and Chavis, 2000; Bruce-Keller et al., 2000, 2001; Vegeto et al., 2000, 2001; Baker et al., 2004; Dimayuga et al., 2005; Johnson and Sohrabji, 2005; Liu et al., 2005).

Astrogliosis is also regulated by estradiol. Depending on the region of the central nervous system and on the pathological condition, estradiol decreases or increases the number of astrocytes. Thus, the hormone decreases astrocytosis in the cerebral cortex and the hippocampus after stab wound injuries (Garcia-Estrada et al., 1993, 1999; Barreto et al., 2007, 2009; López Rodríguez et al., 2011), in

the basal forebrain after an immunotoxic lesion of cholinergic neurons (Martinez and de Lacalle, 2007), in the hippocampus after the administration of kainic acid (Ciriza et al., 2004b) and in the substantia nigra pars compacta in a Parkinson's disease animal model (Tripanichkul et al., 2006). In contrast, the combined treatment of estradiol and progesterone increases the proliferation of astrocytes in the corpus callosum after the induction of demyelination by cuprizone (Acs et al., 2009; Kipp and Beyer, 2009). Furthermore, estradiol increases astrocytosis in the spinal cord after mechanical injury (Ritz and Hausmann, 2008) and in the olfactory bulb after excitotoxic injury (Lewis et al., 2008). The causes for these differences in the effect of estradiol on reactive astrocytes are unknown. However, the effect of gonadal hormones on the number of reactive astrocytes in the cuprizone demyelination model is correlated with an increase in the levels of insulin-like growth factor-I (IGF-I), a trophic factor produced by astrocytes that promotes oligodendrocyte proliferation and differentiation (Acs et al., 2009; Kipp and Beyer, 2009). Thus, while under some circumstances estradiol reduces astrogliosis and the expression of proinflammatory molecules by astrocytes (Kipp et al., 2007; Tenenbaum et al., 2007; Dodel et al., 1999; Cerciat et al., 2010; Rubio et al., 2011), in other conditions the hormone increases astrogliosis and the glial production of trophic factors that promote neuronal survival and remyelination (Sortino et al., 2004; Dhandapani et al., 2005; Kipp and Beyer, 2009).

Role of steroid metabolism and signaling mechanisms involved in the regulation of reactive gliosis by gonadal hormones

Gonadal hormones are metabolized by neural tissue to neuroactive steroids that act by a variety of signaling mechanisms (Garcia-Segura and Melcangi, 2006; Melcangi et al., 2008). These metabolites may mediate some of the effects of gonadal hormones in the nervous system, including the control of reactive gliosis. For instance, the control exerted by progesterone on reactive gliosis may be in part mediated by its reduced metabolites, such as allopregnanolone (Ciriza et al., 2004a; Djebaili et al., 2005; Ciriza et al., 2006; VanLandingham et al., 2007), which modulates the activity of $GABA_A$ receptors (Belelli et al., 2006). Allopregnanolone reduces reactive gliosis in different brain injury models (Ciriza et al., 2004a; Djebaili et al., 2005; Ciriza et al., 2006; VanLandingham et al., 2007) and the inhibition of progesterone metabolism to allopregnanolone blocks the antigliotic action of the hormone in rats injected with kainic acid (Ciriza et al., 2006).

The effect of testosterone on reactive astroglia and reactive microglia after a stab wound injury in the brain may also be in part mediated by its metabolites. Testosterone is converted to estradiol, a ligand of estrogen receptors, by the enzyme aromatase and to dihydrotestosterone (DHT), a ligand of androgen receptor, by the enzyme 5α-reductase. Both enzymes are expressed in the CNS (Martini et al., 1996). The treatment of orchidectomized rats with testosterone reduces the number of reactive astrocytes and reactive microglia in the border of a penetrating lesion in the hippocampus. This effect is observed both when the treatment is initiated immediately after the injury and when it is initiated five days later (Barreto et al., 2007). The effects of testosterone on reactive astrocytes and reactive microglia are fully reproduced by estradiol (Barreto et al., 2007). In contrast, the non-aromatizable testosterone metabolite DHT reproduces the effect of testosterone on reactive microglia but not on reactive astrocytes and only when the treatment with DHT is initiated immediately after injury (Barreto et al., 2007). These findings suggest that the antigliotic action of testosterone in this model may be mediated by its metabolites and mainly by its conversion to estradiol.

The antigliotic effects of the testosterone precursor DHEA may also be mediated by its metabolites. For instance, the inhibition of aromatase blocks the effect of DHEA on reactive astrocytes in the olfactory bulb (Hoyk et al., 2004), suggesting that the antigliotic action of DHEA in this brain region is mediated by estrogens. Another metabolite of DHEA that reduces the inflammatory response of glial cells is 5-androsten-3β, 17β-diol (ADIOL), which is a selective modulator of estrogen receptor (ER)β (Saijo et al., 2011).

In vitro studies have shown that both ERα and ERβ selective agonists reduce the inflammatory response of microglia to LPS (Smith et al., 2011). However, in general, estrogenic compounds with a predominant ERβ profile are more potent in reducing the inflammatory response of astrocytes and microglia *in vitro* (Lewis et al., 2008). Furthermore, estradiol has anti-inflammatory actions in the murine microglial cell line BV-2, which express ERβ and not ERα (Baker et al., 2004) and, as previously mentioned, the ERβ agonist ADIOL reduces the inflammatory response of microglia and astroglia *in vitro* (Saijo et al., 2011). These findings indicate that ERβ is involved in the control of inflammation exerted by estradiol acting directly on astrocytes and microglia. In addition, ERα is also involved in the actions of estradiol on microglia and astrocytes. Thus, the anti-inflammatory actions of estradiol on microglia after intracerebral injection of LPS are lost in ERαKO mice (Vegeto et al., 2003). In addition, expression of ERα in astrocytes mediates the anti-inflammatory actions of estradiol on experimental autoimmune encephalomyelitis (Tiwari-Woodruff et al., 2007; Spence et al., 2011). Therefore, ERα participates in the anti-inflammatory actions of estradiol in the CNS *in vivo*.

The action of ERα on the control of neural inflammation is mediated by the regulation of NFkappaB-mediated transcription of inflammatory molecules. Thus, the activation of ERα results in the inhibition of NFkappaB nuclear translocation in macrophages and microglia by a mechanism mediated by phosphatidylinositol 3-kinase (Ghisletti et al., 2005; Pozzi et al., 2006). In addition, ERα is also involved in the direct repression of NFkappaB-dependent transcription in astrocytes (Giraud et al., 2010). In contrast, ADIOL and other ERβ ligands reduce the expression of proinflammatory genes by inducing the recruitment of the transcriptional corepressor c-terminal binding protein (CtBP) to proinflammatory promoters (Saijo et al., 2011). Therefore, ERα and ERβ control the inflammatory response of glial cells by complementary mechanisms. It is possible that the relative role of ERα and ERβ on the control of the neural inflammatory response *in vivo* would depend both on the type of injury and on the CNS region considered.

Perspectives for the future

Recent studies have identified additional molecules that participate in the control of reactive gliosis by gonadal hormones. However, the mechanisms involved in the interaction of gonadal hormones with these molecules remain to be explored and characterized. One of such molecules is the product of the Parkinson's disease related gene parkin. The control of astrogliosis and microgliosis exerted by estradiol *in vitro* is lost in midbrain cultures from parkin null mice (Rodríguez-Navarro et al., 2008). Parkin may mediate the action of estradiol on gliosis by the regulation of ERα turnover (Rodríguez-Navarro et al., 2008), by enhancing anti-inflammatory IGF-I signaling (Bellini et al., 2011; Akundi et al., 2012) or by regulating the expression of mitochondrial proteins (Pilsl and Winklhofer, 2012).

The endocannabinoid system has also been recently identified as one of the targets of estradiol for the regulation of reactive gliosis. The hormone increases the expression of CB2 receptors and regulates the expression of some of the enzymes involved in the synthesis and metabolism of endocannabinoids in the cerebral cortex after brain injury (López Rodríguez et al., 2011). In addition, both CB1 and CB2 receptor antagonists reduce the action of estradiol on reactive astrocytes in the injured cerebral cortex (López Rodríguez et al., 2011). The precise mechanisms of the interaction of estradiol with the endocannabinoid system in the regulation of reactive gliosis remain to be elucidated. The interaction of estradiol with other signaling molecules that regulate reactive gliosis, such as purinergic receptors (Crain and Watters, 2010), merits also to be explored.

Another important question that needs to be clarified is the participation of peripheral inflammation on the regulation of gliosis by gonadal hormones. For instance, it has been shown that the putative membrane estrogen receptor G protein-coupled receptor 30 (GPR30) contributes to the control of inflammation in experimental autoimmune encephalomyelitis by actions on peripheral immune cells (Blasko et al., 2009). Thus, the final effect of gonadal hormones on the control of reactive gliosis and CNS inflammation may result from a combination of central and peripheral actions.

The existence of sex differences in the response of glial cells to inflammatory and neurodegenerative conditions is also a highly relevant issue, because glial cells may contribute to sex differences in the manifestation of neurodegenerative diseases. This question has recently received some attention and sex differences in the response of astrocytes and microglia to neurodegeneration and inflammation as well as sex differences in the regulation of reactive gliosis by gonadal hormones have been reported (Dasgupta et al., 2005; Doherty et al., 2007; Liu et al., 2007; Cordeau et al., 2008; Crain and Watters, 2010; Santos-Galindo et al., 2011; Sundar Boyalla et al., 2011). However, further studies are required to determine the precise mechanisms and the functional consequences of the sex differences in the response of glial cells under pathological conditions.

Another relevant point is whether aging affects the antigliotic activity of gonadal hormones. Aging *per se* affects glial cells (Godbout and Johnson, 2009). Thus, microglia cells from aged animals exhibit an altered inflammatory profile (Sierra et al., 2007) and the astroglial response after brain injury is enhanced in aged animals (Barreto et al., 2009). The regulation of inflammatory molecules by estradiol in the CNS is also affected by aging (Nordell et al., 2003; Johnson and Sohrabji, 2005) and this may impair the neuroprotective actions of the ovarian hormone in older animals. However, estradiol and other estrogenic compounds are still able to reduce the number of reactive astrocytes in aged animals and in a rat model of menopause, even after a long period of ovarian hormone deprivation (Lei et al., 2003; Barreto et al., 2009).

The most important question that remains to be clarified is the functional outcome of the regulation of reactive gliosis by gonadal hormones. Reactive astrocytes release different molecules that promote neuronal survival, such as IGF-I (Acs et al., 2009; Kipp and Beyer, 2009), transforming growth factor beta (Sortino et al., 2004; Dhandapani et al., 2005) and neuroprotective steroids, including estradiol (Garcia-Ovejero et al., 2005; Garcia-Segura and Melcangi, 2006). Therefore, in addition to decrease local inflammation, the downregulation of reactive gliosis by gonadal hormones after some forms of CNS injury may also potentially reduce the local production and release of neuroprotective factors by reactive astrocytes. Further studies aimed to the identification of the molecular phenotype of the astrocytes and microglia regulated by gonadal hormones after CNS injury are necessary.

Finally, although gonadal hormones regulate gliosis, their therapeutic use to reduce brain inflammation is limited by their peripheral effects, in particular for estradiol and testosterone. For this reason, the antigliotic activity of hormone analogs, such as different selective estrogen receptor agonists or modulators and non-feminizing estrogens, is currently under study (Saijo et al., 2011; Smith et al., 2011; Arevalo et al., 2012).

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